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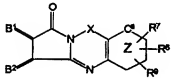

(VI)

(a)

(57) Abstract

Fulgimide derivatives are provided having formula (VI) or stereoisomers thereof, wherein R^7, R^8 and R^9 are hydrogen or are chosen to provide desired solubility, reactivity and spectral properties to the compound; X is a group $-(CH_2)_n-$ or a group (a): in which case it links via a two or three atom chain with carbon atom C^a of ring Z to form a fused bicyclic aromatic ring which may be optionally substituted and n is 0 or 1; Z is an optionally substituted six–membered aromatic or fused bicyclic aromatic ring containing carbon atoms and optionally no more than two atoms selected from oxygen, nitrogen and sulphur. The compounds are useful for imparting photochromic properties to materials by covalent and non–covalent association.

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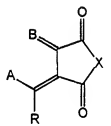
Photochromic Compounds

The present invention relates to a group of compounds which exhibit photochromism, their preparation and use as optical switches for luminescent materials. In particular, the invention relates to fulgimide derivatives.

Photochromism can be defined as the property of a material able to change reversibly its visible absorption spectrum upon exposure to activating radiation and to revert to its original absorption spectrum thermally on removal of the activating radiation, or on exposure to radiation of a different wavelength.

US Patent No.4220708 describes a series of photochromic succinic anhydride and succinimide derivatives (fulgides and fulgimides respectively) having the following general formula (I):

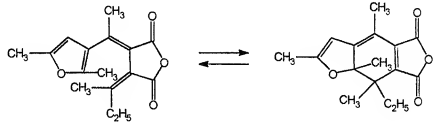


(I)

wherein X represents O, NR^6, R^6 being H, alkyl, aryl or an aralkyl group;
R represents an alkyl, aryl, aralkyl, or heterocyclic group;
A represents a 3-furyl, 3-thienyl, 3-benzofuryl or 3-benzothienyl group;
B represents a cycloalkylidene group or the group,

in which R^2 and R^3 independently represent an alkyl, aryl, aralkyl or a heterocyclic group, or one of R^2 and R^3 represents hydrogen and the other represents an alkyl, aryl, aralkyl, or heterocyclic group.

Compounds of this class undergo cyclisation when exposed to ultraviolet radiation, ring closure taking place between the carbon atom to which groups R^2 and R^3 are attached and the 2-position of the furyl or thienyl ring. The photocyclisation reaction for fulgide ring structures is illustrated by the following scheme (Scheme 1).



(II) (III)

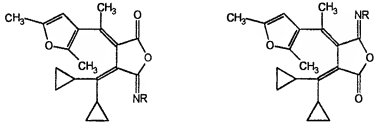
Scheme 1

The cyclic forms of the fulgides, for example (III), are highly coloured, usually in the bright red to deep purple range and this is reported to arise from the extended, near planar, conjugated double bond structure with the oxygen heteroatom at one end of the molecule and the conjugated carbonyl at the other.

Compounds of formula (I) in which X is oxygen may be converted into the corresponding fulgimide derivatives (I, X = NR^6) by reaction of the anhydride with a primary amine followed by an acid chloride in a suitable solvent such as dichloromethane.

As with the fulgides, fulgimides undergo photochemical ring closure to form the more highly coloured, thermally stable product. They exhibit photochromic properties similar to the corresponding fulgides, except that the long wavelength (visible) absorption bands of the coloured forms are generally broader and show bathochromic shifts. Furthermore fulgimides display greater resistance to hydrolysis compared with fulgides. Suitable fulgimide derivatives may be coupled with target biological systems, thereby giving such a system photochromic properties. For example, a fulgimide derivative in which R^6 = CH_2COOH was coupled via its N-hydroxysuccinimide ester to the nucleotide analogue, aminoallyl-2'-deoxyuridine 5'-triphosphate (V.Kiruvanayagam, PhD Thesis, University of Wales, (1995), p137).

Replacement of one or the other of the carbonyl groups of the fulgide structure with a substituted nitrogen results in two alternative isomers of fulgimides, termed α-isofulgimides (IV) and β-isofulgimides (V). The compounds undergo photochemical ring closure to give coloured forms.



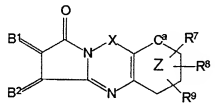
α-Isofulgimide (IV)

β-Isofulgimide (V)

α-Isofulgimides may be prepared by the reaction of the appropriate succinic half-ester derivative with the Grignard derivative of the required amine, followed by cyclisation with DCC. β-Isofulgimides can be prepared by a similar method,

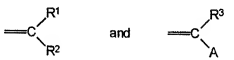
but a more convenient approach is to derive the required succinamic acid from the corresponding fulgide, followed by reaction with DCC (K.S.V.Koh, PhD Thesis, University of Wales, 1993).

Accordingly the present invention provides compounds of formula VI:



(VI)

or stereoisomers thereof, wherein groups B^1 and B^2 are selected from the groups:



such that $B^1 \neq B^2$;

R^7, R^8 and R^9 are hydrogen or are chosen to provide desired solubility, reactivity and spectral properties to the compound;

X is a group $-(CH_2)_n-$ or a group:

in which case it links via a two or three atom chain with carbon atom C^a of ring Z to form a fused bicyclic aromatic ring which may be optionally substituted and n is 0 or 1;

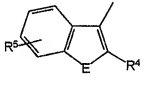
Z is an optionally substituted six-membered aromatic or fused bicyclic aromatic ring containing carbon atoms and optionally no more than two atoms selected from oxygen, nitrogen and sulphur;

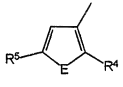
R^1 and R^2 independently represent an alkyl, cycloalkyl, aryl, or an aralkyl group or one of R^1 and R^2 represents hydrogen and the other an alkyl, cycloalkyl, aryl, or an aralkyl group, or the group:

represents an adamantylidene group;

R^3 represents hydrogen, alkyl, or aryl;

A represents a substituted or unsubstituted heterocyclic ring having one of the following structures:





where R^4 is selected from hydrogen, alkyl, aryl, and aralkyl groups, and R^5 is selected from hydrogen, C_{1-12} hydrocarbyl optionally substituted with halogen, C_{1-6} alkoxy, aryl and C_{6-12} aryloxy groups and E is selected from O, S and NR^6, where R^6 is selected from hydrogen, C_{1-6} alkyl, aryl or an aralkyl group.

Suitably, the two or three atom chain which links group X with carbon atom C^a of ring Z contains carbon atoms and optionally no more than one nitrogen atom. Preferably the two or three atom chain contains carbon atoms.

Optional substituents R^7, R^8 and R^9 on the aromatic ring Z or the bicyclic aromatic ring that incorporates Z are the same or different and are independently selected from $-R^{10}$ and $-L-R^{10}$, wherein R^{10} is selected from:

neutral groups that reduce water solubility; polar groups that increase water solubility; target bonding groups such as functional groups that can be used in labelling reactions; reactive groups; electron donating and withdrawing groups that shift the emission wavelengths of the photochromic molecule; lipid and hydrocarbon solubilising groups, and L is selected from the group consisting of a straight or branched C_{1-10} alkyl chain, a C_{2-10} monoether or polyether and a C_{2-10} atom chain containing up to two secondary amide linkages.

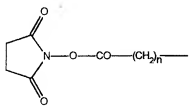
Preferred R^{10} groups are selected from: hydrogen, halogen, amide, C_1-C_6 alkoxy, cyano, aryl, heteroaryl, sulphonate, quaternary ammonium, hydroxyl, optionally substituted amino, sulphydryl, carbonyl, and reactive groups, for example, succinimidyl ester and anhydride, and groups reactive with amino, hydroxyl, carboxyl, aldehyde, or sulphydryl groups.

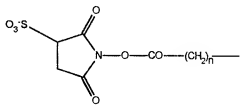
Specific examples of the reactive groups R^7, R^8 and R^9 and the groups with which R^7, R^8 and R^9 will react are provided in Table 1. In the alternative, the R^7, R^8 and R^9 may be the functional groups of Table 1 which would react with the reactive groups of a target molecule.

Table 1: Possible Reactive Substituents and Functional Groups Reactive Therewith

Reactive Groups	**Functional Groups**
succinimidyl esters	primary amino, secondary amino
anhydrides	primary amino, secondary amino, hydroxyl
substituted hydrazines,	aldehydes, ketones
acid halides	amino groups
haloacetamides, maleimides	thiols, imidazoles, hydroxyl, amine
carbodiimides	carboxyl groups
phosphoramidites	hydroxyl groups

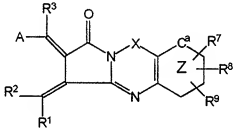
Preferred reactive groups R^7, R^8 and R^9 which are especially useful for labelling target components with available amino and hydroxyl functional groups include:





where n is 0 or an integer from 1-10.

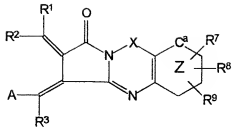
In one preferred embodiment of the present invention the compounds of formula (VI) have the formula (VIa):



(VIa)

or a stereoisomer thereof, wherein groups R^1, R^2, R^3, R^7, R^8, R^9, A, X and Z are hereinbefore defined.

In a second preferred embodiment of the present invention the compounds of formula (VI) have the formula (VIb):



(VIb)

or a stereoisomer thereof, wherein groups R^1, R^2, R^3, R^7, R^8, R^9, A, X and Z are hereinbefore defined.

In one embodiment of the present invention R^6 is selected from hydrogen, C_{1-6} alkyl, or aralkyl group and L is selected from the group consisting of a straight or branched C_{1-10} alkyl chain, and a C_{2-10} monoether or polyether.

Alkyl is a straight or branched chain alkyl group containing from 1-20 carbon atoms, preferably 1 to 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl and butyl.

Aryl is an aromatic substituent containing one or two fused aromatic rings containing 6 to 10 carbon atoms, for example phenyl or naphthyl, the aryl being optionally and independently substituted by one or more substituents, for example halogen, straight or branched chain alkyl groups containing 1 to 10 carbon atoms, cycloalkyl, aralkyl and alkoxy for example methoxy, ethoxy, propoxy and n-butoxy.

Cycloalkyl is an alicyclic substituent containing from 3 to 6 carbon atoms being attached by a single bond, for example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Heteroaryl is a mono- or bicyclic 5 to10 membered aromatic ring system containing at least one and no more than 3 heteroatoms which may be selected from N, O, and S and is optionally and independently substituted by one or

more substituents, for example halogen, straight or branched chain alkyl groups containing 1 to 20 carbon atoms, cycloalkyl, aralkyl and alkoxy for example methoxy, ethoxy, propoxy and n-butoxy.

Aralkyl is a C_1 to C_6 alkyl group substituted by an aryl or heteroaryl group.

Halogen and halo groups are selected from chlorine, bromine and iodine.

For the purpose of increasing water solubility or reducing unwanted non-specific binding of the photochromic compounds of the present invention to inappropriate components of a sample, one or more of the R^7, R^8 and R^9 groups may be selected from well known polar or electrically charged chemical groups. Examples of such groups are -S-F, where F is hydroxy, sulphonate, carboxylate, substituted amino or quaternary amino and where S is a spacer group such as $-(CH_2)_n-$ where n is 0 to 6. Examples of -S-F groups include C_{1-6} alkyl sulphonates, such as $-(CH_2)_3-SO_3^-$ and $-(CH_2)_4-SO_3^-$.

Specific examples of the compounds of the present invention are as follows:

i) E-4-Dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

ii) E-4-Diphenylmethylene-3-[1-(2,5-dimethyl-3-thienyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

iii) E-4-Dicyclopropylmethylene-7,8-dimethyl-3-[1-(2-methyl-5-phenyl-3-thienyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

iv) E-3-Adamantylidene-7,8-dimethyl-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

v) E-3-Adamantylidene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid;

vi) E-8-Amino-4-dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

vii) Z-4-Adamantylidene-8-nitro-3-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

viii) Phenacyl Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylate;

ix) E-3-Dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid.

The groups provided herein are not intended to be all-inclusive of those groups which can be incorporated at the R^7, R^8 and R^9 sites of the present invention. It will be understood that there are various other groups which will react with groups on material that is to be labelled by the compounds of the present invention. Compounds produced by the incorporation of other such groups at the R^7, R^8 and R^9 sites are intended to be encompassed by the present invention.

The compounds of the present invention may be used in one or more biological and non-biological applications. With respect to non-biological applications, compounds of the present invention having one or more uncharged groups at the R^7, R^8 and R^9 positions, for example alkyl and aryl moieties, may be dissolved in non-polar materials to provide photochromic properties to those materials. Such non-polar materials include, for example paints, polymers, plastics, waxes, oils, inks and hydrocarbon solvents. Another non-biological application of the photochromic compounds of the present invention is to dissolve compounds having one or more charged and/or polar groups at the R^7, R^8 and R^9 positions in polar solvents such as water, alcohols such as methanol or ethanol, ethylene glycol, or mixtures of such solvents.

Alternatively, the photochromic compounds of the present invention may contain a polymerizable group suitable for the formation of a polymer containing the complex. Suitable polymerizable groups are selected from acrylate, methacrylate and acrylamide. Polymerization may be carried out with a

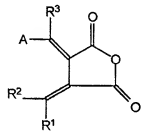
suitably derivatized compound of this invention used in conjunction with a second polymerizable monomer starting material, such as styrene or vinyltoluene, to form a copolymer containing the photochromic compound. The photochromic compounds need not have a polymerisable group, for example, the complex may be incorporated during polymerisation or particle formation or may be absorbed into or onto polymer particles.

Compounds of the present invention having a functional or reactive group at the R^7, R^8 and R^9 positions may be used to covalently label a target material to impart photochromic properties to the target material, such as a carrier material, a luminescent compound or a biological material. The target bonding group may be a reactive group for reacting with a functional group on the target material. Alternatively the target bonding group may be a functional group for reaction with a reactive group on the target.

Suitable target materials may include a luminescent compound, such as fluorescent dyes (based for example on the fluorescein, rhodamine, coumarin, pyrene and cyanine chromophores), antibodies, antigens, proteins, carbohydrates, lipids, nucleotides which contain or are derivatized to contain one of amino, hydroxyl, sulphydryl, carboxyl, or carbonyl groups, and oxy or deoxy polynucleic acids which contain or are derivatized to contain one of amino, hydroxyl, phosphate, thiophosphoryl, sulphydryl, carboxyl, or carbonyl groups, cells, polymer particles, or glass beads. Covalent labelling using compounds of the present invention may be accomplished with a target having at least one functional or reactive group as defined hereinbefore. The target may be reacted with an amount of a compound of the present invention having at least one of R^7 to R^9 that includes a reactive or functional group as hereinbefore defined that can covalently bind with the functional or reactive group of the target material. The target material and the compound of the present invention are incubated under conditions and for a period of time

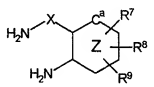
sufficient to permit the target material to covalently bond to the compound of the present invention.

The present invention also provides a process for the preparation of a compound of formula (VI) which comprises reaction of a compound of formula (VII),



(VII)

or its corresponding di-carboxylic acid, di-C_1 - C_6 alkyl ester, or mono-carboxylic acid-mono C_1 - C_6 alkyl ester derivative, wherein R^1, R^2, R^3 and A are as hereinbefore defined with a compound of formula (VIII):



(VIII)

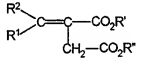
or a salt thereof, optionally substituted by groups R^7, R^8 and R^9, wherein R^7, R^8 and R^9, X and Z are as hereinbefore defined. The reaction is suitably carried out in a dry, inert solvent such as toluene and in the absence of light. The reaction is suitably carried out at an elevated temperature, for example 50°C to 150°C, suitably 100°C to 125°C. The reaction mixture (containing a mixture of

geometric isomers of the product) is fractionated into separate isomers by column chromatography using silica gel, or by fractional crystallisation.

The Stobbe condensation provides a general method for preparing compounds of the general formula (VII). An account of this reaction and its application to the synthesis of a wide range of succinic acid derivatives is given in Organic Reactions, Vol. 6, pp1-73, published by Wiley, New York 1951. For example, compounds of formula (VII) can be prepared by reaction of a compound of formula (IX),

(IX)

wherein R^3 and A are as hereinbefore defined with a succinic ester of formula (X),



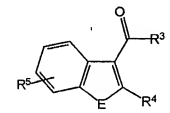
(X)

where R^1 and R^2 are as hereinbefore defined and R' and R'' are independently selected from methyl, ethyl, n-propyl, and n-butyl, by a Stobbe condensation to yield a product of formula (VII). Preferably the Stobbe condensation may be carried out by treating the reactants in t-butanol, or toluene, or tetrahydrofuran containing potassium t-butoxide. The product at this stage is the half-ester, ie where one of the R' or R'' groups is hydrogen. The half-ester is then converted into the di-acid by hydrolysis, for example by boiling with ethanolic potassium

hydroxide. The di-acid is then converted into its anhydride by a dehydration reaction, for example by stirring at ambient temperature with an acid chloride. Preferably acetyl chloride is used for this purpose.

For example:

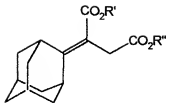
(i) Compounds of formula (VII) can be prepared using as the starting material a ketone of formula (XI),



(XI)

wherein R^3, R^4 , R^5 and E are as hereinbefore defined with a succinic ester of formula (X), where R^1, R^2 , R' and R'' are hereinbefore defined.

(ii) Compounds of formula (VII) above can also be prepared in an analogous manner to that described above using adamantan-2-one as a starting material. Preparation of adamantan-2-one is described in US Patent No. 3257456 and by Gulak et al, Organic Synthesis, 53, 8, (1973). Compounds of formula (VII) can be prepared by refluxing adamantan-2-one with a succinate diester in a solution of potassium t-butoxide in t-butanol to give the potassium salt of the corresponding half ester, which is converted into an adamant-2-ylidene succinate diester of formula (XII), in which R' and R'' are hereinbefore defined.



(XII)

Compounds of formula (VII) containing an adamantylidene group are obtained by reacting a diester of formula (XII) with a ketone of formula (IX) or of formula (XI) in the presence of sodium hydride or potassium *t*-butoxide, in a dry inert solvent such as toluene. See for example, US Patent No.4220708, the disclosure of which is incorporated by reference.

Precursor compounds of formula (VIII) are readily available or may be prepared by methods well known to those skilled in the art.

It will be readily appreciated that certain compounds of formula (VI) may be useful as intermediates for conversion to other compounds of the formula (VI) by methods well known to those skilled in the art. Likewise, certain of the intermediates may be useful for the synthesis of derivatives of formula (VI). The compounds of the present invention may be synthesized by the methods disclosed herein. Derivatives of the compounds having a particular utility are prepared either by selecting appropriate precursors or by modifying the resultant compounds by known methods to include functional groups at a variety of positions. As examples, the compounds of the present invention may be modified to include certain reactive groups for preparing a photochromic labelling reagent, or charged or polar groups may be added to enhance the solubility of the compound in polar or nonpolar solvents or materials. As examples of conversions, carboxylic acid groups may be converted into esters, and amide groups.

Compounds of the present invention switch from near colourless to coloured forms on exposure to UV light and the colour of the coloured form is pH dependent.

The invention is further exemplified by reference to the following examples and Figure 1 which illustrates a fluorescence study of a photochromic compound-fluor switch according to Example 11.

Experimental Section

i) General

Ultraviolet spectra were recorded on a Cecil CE6600 spectrophotometer and a Perkin Elmer Lambda 20 UV/Vis spectrophotometer, using UV Winlab, for 1 x 10^{-4}M solutions in dry toluene.

^{1}H NMR spectra were obtained using a Bruker WM 400 (400MHz) or a Bruker WM 360 (360MHz) FT NMR spectrometer for samples in deuterated chloroform with 1% TMS as internal standard.

Microanalyses were obtained using a Perkin Elmer 240B analyser.

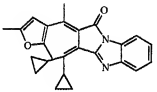
Melting points were measured on a Reichert Hot Stage Microscope.

Photochemical reactions employed an optical bench incorporating a focussed medium pressure 100W mercury arc lamp and either a Woods glass OX1A filter to produce 366nm light or a 370nm cut-off yellow filter for bleaching.

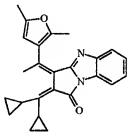
ii) General Synthesis of Compounds of Formula (VI)

A solution of a compound of formula (VII) and a compound of formula (VIII) in toluene was boiled (24 hours) in the absence of light. Solvent was removed under reduced pressure and the residual oil was purified by column chromatography on silica gel, using usually mixtures of diethyl ether and petroleum ether (40-60°C) as eluant. The main fractions gave compounds of formula (VI) usually as yellow crystals after recrystallisation from diethyl ether and petroleum ether (40-60°C).

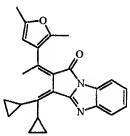
Example 1: Preparation of Compounds 1a, 1b and 1c



1a



1b



1c

A solution of E/Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]succinic anhydride (5.00g, 16.03mmol) and 1,2-phenylenediamine (2.08g, 19.23mmol) in toluene (50ml) was boiled for 23 hours. Removal of solvent left an oil consisting of a mixture of compounds of formula 1a, 1b and 1c, which were separated and purified by column chromatography and by fractional recrystallisation from diethyl ether and petroleum ether (40-60°C).

1a: E-4-Dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Yellow crystals (0.81g, 13%), m.p. 148-149°C, m/z 384.2. Found: C, 78.15; H, 6.22; N, 7.19%. $C_{26}H_{24}N_2O_2$ requires C, 78.10; H, 6.25; N, 7.29%.

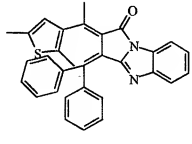
1b: Z-3-Dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Yellow crystals (0.65g, 11%), m.p. 192-194°C, m/z 384.2. Found: C, 77.92; H, 6.44; N, 7.13%. $C_{26}H_{24}N_2O_2$ requires C, 78.10; H, 6.25; N, 7.29%.

1c: Z-4-Dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Yellow crystals (0.25g, 4%), m.p. 214-216°C, m/z 384.2. Found: C, 78.05; H, 6.37; N, 7.04%. $C_{26}H_{24}N_2O_2$ requires C, 78.10; H, 6.25; N, 7.29%.

Example 2: Preparation of Compound 2



2

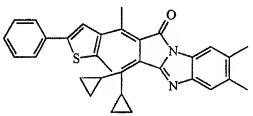
A solution of E-[1-(2,5-dimethyl-3-thienyl)ethylidene]diphenylmethylene succinic anhydride (0.50g, 1.25mmol) and 1,2-phenylenediamine (0.16g, 1.48mmol) in toluene (30ml) was boiled for 68 hours. Removal of solvent left an oil

containing the impure compound of formula 2, which was purified by column chromatography and by fractional recrystallisation from diethyl ether and petroleum ether (40-60°C).

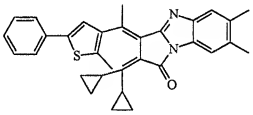
2: E-4-Diphenylmethylene-3-[1-(2,5-dimethyl-3-thienyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Yellow crystals (0.25g, 42%), m.p. 224-225.5°C, m/z 472.1. Found: C, 78.78; H, 5.32; N, 6.01%. $C_{31}H_{24}N_2OS$ requires C, 78.79; H, 5.12; N, 5.93%.

Example 3: Preparation of Compounds 3a and 3b



3a



3b

A solution of E-3-dicyclopropylmethylene-4-[1-(2-methyl-5-phenyl-3-thienyl)ethylidene] succinic anhydride (1.00g, 2.56mmol) and 4,5-dimethyl-1,2-phenylenediamine (0.42g, 3.08mmol) in toluene (40ml) was boiled for 69 hours. Removal of solvent left an oil consisting of a mixture of compounds of formula 3a and 3b, which were separated and purified by column chromatography and by fractional recrystallisation in diethyl ether and petroleum ether (40-60°C).

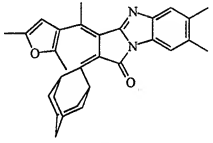
3a: E-4-Dicyclopropylmethylene-7,8-dimethyl-3-[1-(2-methyl-5-phenyl-3-thienyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one

Green/yellow crystals (0.16g, 13%), m.p. 213.5-215.5°C, m/z 490.0. Found: C, 78.30; H, 6.20; N, 5.65%. $C_{32}H_{30}N_2OS$ requires C, 78.33; H, 6.16; N, 5.71%.

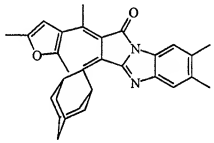
3b: Z-3-Dicyclopropylmethylene-7,8-dimethyl-3-[1-(2-methyl-5-phenyl-3-thienyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one

Pale yellow crystals (0.28g, 22%), m.p. 233-236°C, m/z 490.1. Found: C, 78.12; H, 6.34; N, 5.78%. $C_{32}H_{30}N_2OS$ requires C, 78.33; H, 6.16; N, 5.71%.

Example 4: Preparation of Compounds 4a and 4b



4a



4b

A solution of E-3-adamantylidene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]succinic anhydride (1.00g, 2.84mmol) and 4,5-dimethyl-1,2-phenylenediamine (0.58g, 4.26mmol) in toluene (40ml) was boiled for 22 hours. Removal of solvent left an oil consisting of a mixture of compounds of formula 4a and 4b, which were separated and purified by column chromatography and by fractional recrystallisation in diethyl ether and petroleum ether (40-60°C).

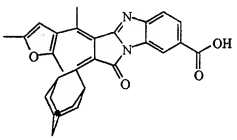
4a: E-3-Adamantylidene-7,8-dimethyl-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Yellow/Green cube shaped crystals (0.26g, 20%), m.p. 243-244°C, m/z 452.3. Found: C, 79.84; H, 6.91; N, 6.09%. $C_{30}H_{32}N_2O_2$ requires C, 79.61; H, 7.13; N, 6.19%.

4b: E-4-Adamantylidene-7,8-dimethyl-3-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one

Colourless crystals (which turned blue on surface) (0.08g, 6%), m.p. 221-223°C, m/z 452.3. Found: C, 79.35; H, 7.25; N, 6.24%. $C_{30}H_{32}N_2O_2$ requires C, 79.61; H, 7.13; N, 6.19%.

Example 5: Preparation of Compound 5



5

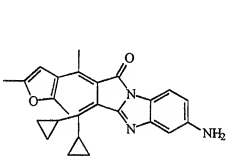
A solution E-3-adamantylidene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]succinic anhydride (1.00g, 2.84mmol), 3,4-diaminobenzoic acid (0.52g, 3.42mmol) and a catalytic amount of potassium tert butoxide (0.032g, 2.85×10^{-4}mol) in toluene (30ml) were boiled for 49 hours. Removal of solvent left an oil containing the impure compound of formula 5, which was purified by column chromatography using ethyl acetate and petroleum ether (40-60°C) followed by fractional recrystallisation in a hot 50%:50% toluene/ethanol solution.

5: E-3-Adamantylidene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol-[1,2-a]pyrrolidin-2-one-8-carboxylic acid

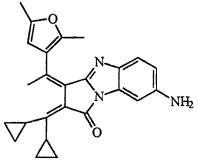
Yellow/white powder (0.16g, 12%), m.p. 271-273°C, m/z 468.2.

Found: C, 74.12; H, 6.15; N, 5.68%. $C_{29}H_{28}N_2O_4$ requires C, 74.34; H, 6.02; N, 5.98%.

Example 6: Preparation of Compounds 6a and 6b



6a



6b

A solution of E/Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]succinic anhydride (1.50g, 4.81mmol) and 4-amino-1,2-phenylenediamine, [made by the catalytic hydrogenation of 4-nitro-1,2-phenylenediamine (2.00g, 13.07mmol) using Raney nickel and hydrazine (2ml), in toluene (40ml)] was boiled for 96 hours. Removal of solvent left an oil consisting of compounds of formula 6a and 6b, which were separated and purified by column chromatography and by fractional recrystallisation in diethyl ether and petroleum ether (40-60°C). Compound 6b was obtained admixed with small amounts of isomers.

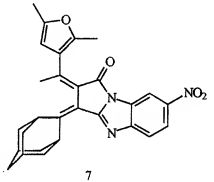
6a: E-8-Amino-4-dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one

Yellow/brown powder (0.11g, 6%), m.p. 91-94°C, m/z 399.4. Found: C, 74.96; H, 6.54; N, 10.71%. $C_{25}H_{25}N_3O_2$ requires C, 75.19; H, 6.27; N, 10.53%.

6b Z-8-Amino-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one

Green powder (0.13g, 7%), m/z 399.5. Found: C, 74.92; H, 6.52; N, 10.62%. $C_{25}H_{25}N_3O_2$ requires C, 75.19; H, 6.27; N, 10.53%.

Example 7: Preparation of Compound 7



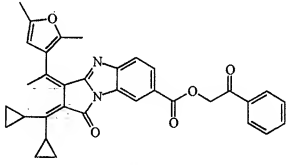
7

A solution of methyl Z-2-adamantylidene-3-[1-(2,5-dimethyl-3-furyl)ethylidene] succinate (0.75g, 1.95mmol) containing 4-nitro-1,2-phenylenediamine (0.33g, 2.15mmol) was boiled in dichloromethane (40ml) with 1-ethyl-3-(3-dimethylamino) propylcarbodiimide hydrochloride (0.82g, 4.28mmol) for 18 hours. Removal of solvent left an oil containing the impure compound of formula 7, which was purified by column chromatography using diethyl ether and petroleum ether (40-60 °C), followed by fractional recrystallisation from dichloromethane and petroleum ether (40-60 °C).

7: Z-4-Adamantylidene-8-nitro-3-[1-(2,5-dimethyl-3-furyl)ethylidene] benzimidazol[1,2-a]pyrrolidin-2-one

Yellow needles (0.20g, 22%), m.p.232-234 °C, m/z 470.4.

Example 8: Preparation of Compound 8



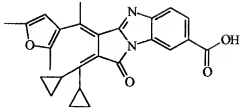
8

A solution of Z/E-4-methyl 2-dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl) ethylidene]succinates (4.50g, 13.08mmol) containing phenacyl 3,4-diamino-benzoate (3.50g, 12.96mmol) was boiled in dichloromethane (50ml) with 1-ethyl-3-(3-dimethylamino) propylcarbodiimide hydrochloride (5.50g, 28.72mmol) for 3 hours. Removal of solvent left an oil containing impure compound of formula 8, which was purified by column chromatography using ethyl acetate and petroleum ether (40-60 °C), followed by fractional recrystallisation from dichloromethane and petroleum ether (40-60 °C).

8: Phenacyl Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene] benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylate

Yellow crystals (1.34g, 18%), m.p.213-215 °C, m/z 547.1.

Example 9: Preparation of Compound 9



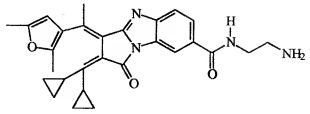
9

Phenacyl Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene] benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylate (2.50g, 4.58mmol) was dissolved in dry dichloromethane (20ml) containing glacial acetic acid (10ml) and stirred. Zinc dust (9g, 0.14mol) was added over a period of 10 minutes and then stirred for 30 minutes. The reaction mixture was filtered, and the filtrate washed with water (4 x 200ml) and dried over anhydrous sodium sulphate. Removal of solvent left an oil containing impure compound of formula 9, which was purified by column chromatography using ethyl acetate and petroleum ether (40-60 °C), followed by fractional recrystallisation from diethyl ether and petroleum ether (40-60 °C).

9: E-3-Dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene] benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid

Yellow/green powder (0.27g, 14%), m.p.234.5-235.5 °C, m/z 428.3. Found: C, 72.74; H, 5.89; N, 6.27%. $C_{26}H_{24}N_2O_4$ requires C, 72.88; H, 5.65; N, 6.54%.

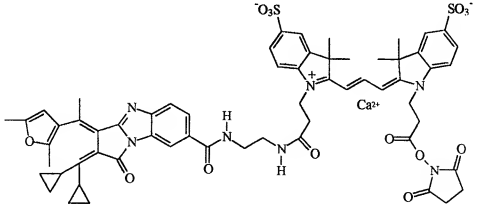
Example 10: Preparation of Compound 10



10

A solution of E-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene] benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid (0.30g, 7.01 x 10^{-4}mol) in dichloromethane (20ml) was stirred under nitrogen with thionyl chloride (0.20ml, 0.33g, 2.74mmol) for 10 minutes. Solvent and excess thionyl chloride was removed on a rotary evaporator. Under nitrogen atmosphere and in the dark, the residual oil dissolved in dichloromethane (20ml) was added dropwise over a period of 1 hour, using a pressure equalising dropping funnel, to a stirred solution of ethylenediamine (0.45ml, 0.40g, 6.73mmol) in dichloromethane (20ml). The reaction mixture was washed with water (2 x 100ml) and dried. Petroleum ether (40-60 °C) was added and the solvent removed on a rotary evaporator until compound of the formula 10 separated out as a light brown powder (0.12g, 36%), m.p.168-179 °C, m/z 471.4.

Example 11: Preparation of Photochrome-Cy3 conjugate (Compound 11)



11

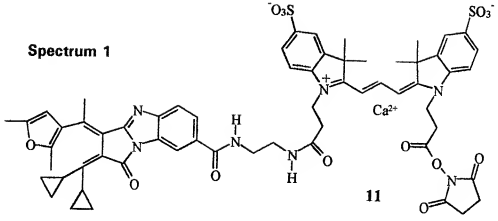
To a stirred solution of bis-functional sulphonated Cy3 dye (Amersham Pharmacia Biotech) (100mg, 1.49 x 10^{-4} mol) in acetonitrile (20ml) was added 1,3-dicyclohexylcarbodiimide (59mg, 2.86 x 10^{-4}mol) and N-hydroxysuccinimide (35mg, 3.04 x 10^{-4}mol). The reaction mixture was stirred in the dark for 18 hours under nitrogen. The reaction mixture was filtered and solvent removed from the filtrate on a rotary evaporator leaving a purple solid (0.107g). A sample of this solid (53mg) was dissolved in dimethylformamide (7ml) and stirred in the dark under nitrogen. To this was added dropwise over 3 hours, a solution of compound of formula 10 (28mg, 5.96 x 10^{-5}mol) in dimethylformamide (2ml). The reaction mixture was stirred for 17 hours and filtered. Solvent was removed from the filtrate on a rotary evaporator and the residual oil dissolved in a minimum amount of methanol and loaded onto a glass backed reverse phase (RP-18-254s) pre-coated preparative plate and separated using a 90% methanol : 10% water eluant system. The appropriate band (RF range 40%-50%) was scratched off the plate washed with methanol to extract product and filtered. Removal of solvents from the filtrate on a rotary evaporator gave compound of formula 11 as a purple solid (23mg).

Fluorescence study of photochromic compound-fluor switch (Scheme 2 and Figure 1)

A solution of compound of formula 11 in methanol had its emission spectrum ($\lambda_{Excitation}$ 550 nm) measured before exposure to UV light (Figure 1, spectrum 1). The emission spectrum ($\lambda_{Excitation}$ 550 nm) of the same sample was measured following irradiation (366 nm) for 2 minutes using a 12W hand lamp incorporating Woods glass filter (Figure 1, spectrum 2). (Note: exposure to UV light causes the ring closure of compound of formula 11 to compound of formula 12, (Scheme 2)).

The emission spectrum ($\lambda_{Excitation}$ 550 nm) of the same sample was measured following bleaching using five flashes from a flash gun mounted with a 370nm cut-off yellow filter (Figure1, spectrum 3). (Note: bleaching with visible light causes ring opening of compound of formula 12 to regenerate the compound of formula 11, (Scheme 2)).

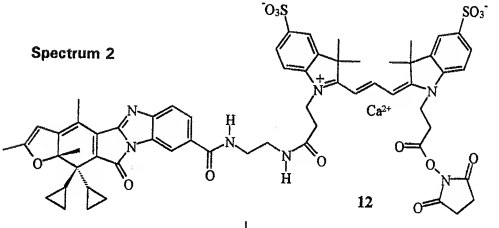
Spectrum 1



11

UV

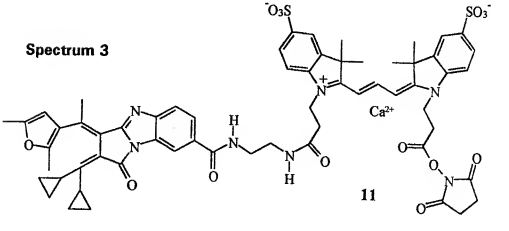
Spectrum 2



12

Visible

Spectrum 3



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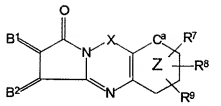
Claims

1. A compound of formula:



or stereoisomers thereof, wherein groups B^1 and B^2 are selected from the groups:

such that $B^1 \neq B^2$;

R^7, R^8 and R^9 are hydrogen or are chosen to provide desired solubility, reactivity and spectral properties to the compound;

X is a group $-(CH_2)_n-$ or a group:

in which case it links via a two or three atom chain with carbon atom C^a of ring Z to form a fused bicyclic aromatic ring which may be optionally substituted and n is 0 or 1;

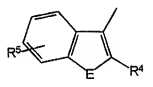
Z is an optionally substituted six-membered aromatic or fused bicyclic aromatic ring containing carbon atoms and optionally no more than two atoms selected from oxygen, nitrogen and sulphur;

R^1 and R^2 independently represent an alkyl, cycloalkyl, aryl, or an aralkyl group or one of R^1 and R^2 represents hydrogen and the other an alkyl, cycloalkyl, aryl, or an aralkyl group, or the group:

represents an adamantylidene group;

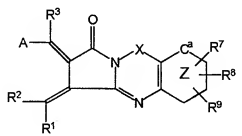
R^3 represents hydrogen, alkyl, or aryl;

A represents a substituted or unsubstituted heterocyclic ring having one of the following structures:



where R^4 is selected from hydrogen, alkyl, aryl, and aralkyl groups, and R^5 is selected from hydrogen, C_{1-12} hydrocarbyl optionally substituted with halogen, C_{1-6} alkoxy, aryl and C_{6-12} aryloxy groups and E is selected from O, S and NR^6, where R^6 is selected from hydrogen, C_{1-6} alkyl, aryl or an aralkyl group.

2. A compound of formula:



or a stereoisomer thereof, wherein groups R^7, R^8 and R^9 are hydrogen or are chosen to provide desired solubility, reactivity and spectral properties to the compound;

X is a group $-(CH_2)_n-$ or a group,

in which case it links via a two or three atom chain with carbon atom C^a of ring Z to form a fused bicyclic aromatic ring which may be optionally substituted and n is 0 or 1;

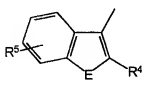
Z is an optionally substituted six-membered aromatic or fused bicyclic aromatic ring containing carbon atoms and optionally no more than two atoms selected from oxygen, nitrogen and sulphur;

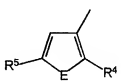
R^1 and R^2 independently represent an alkyl, cycloalkyl, aryl, or an aralkyl group or one of R^1 and R^2 represents hydrogen and the other an alkyl, cycloalkyl, aryl, or an aralkyl group, or the group:

represents an adamantylidene group;

R^3 represents hydrogen, alkyl, or aryl;

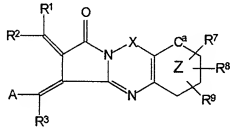
A represents a substituted or unsubstituted heterocyclic ring having one of the following structures:





where R^4 is selected from hydrogen, alkyl, aryl, and aralkyl groups, and R^5 is selected from hydrogen, C_{1-12} hydrocarbyl optionally substituted with halogen, C_{1-6} alkoxy, aryl, and C_{6-12} aryloxy groups and E is selected from O, S and NR^6, where R^6 is selected from hydrogen, C_{1-6} alkyl, aryl or an aralkyl group.

3. A compound of formula:



or a stereoisomer thereof, wherein groups R^7, R^8 and R^9 are hydrogen or are chosen to provide desired solubility, reactivity and spectral properties to the compound;

X is a group $-(CH_2)_n-$ or a group,

in which case it links via a two or three atom chain with carbon atom C^a of ring Z to form a fused bicyclic aromatic ring which may be optionally substituted and n is 0 or 1;

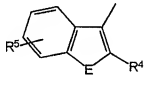
Z is an optionally substituted six-membered aromatic or fused bicyclic aromatic ring containing carbon atoms and optionally no more than two atoms selected from oxygen, nitrogen and sulphur;

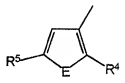
R^1 and R^2 independently represent an alkyl, cycloalkyl, aryl, or an aralkyl group or one of R^1 and R^2 represents hydrogen and the other an alkyl, cycloalkyl, aryl, or an aralkyl group, or the group:

represents an adamantylidene group;

R^3 represents hydrogen, alkyl, or aryl;

A represents a substituted or unsubstituted heterocyclic ring having one of the following structures:





where R^4 is selected from hydrogen, alkyl, aryl, and aralkyl groups, and R^5 is selected from hydrogen, C_{1-12} hydrocarbyl optionally substituted with halogen, C_{1-6} alkoxy, aryl, and C_{6-12} aryloxy groups and E is selected from O, S and NR^6, where R^6 is selected from hydrogen, C_{1-6} alkyl, aryl or an aralkyl group.

4. A compound according to any of Claims 1-3 wherein R^1 and R^2 each independently represent lower alkyl groups including cycloalkyl groups having 1-6 carbon atoms.

5. A compound according to any of Claims 1-3 wherein R^3 represents a lower alkyl group having 1-6 carbon atoms.

6. A compound according to any of Claims 1-3 wherein R^4 represents a lower alkyl group having 1-6 carbon atoms, phenyl or a substituted phenyl group.

7. A compound according to any of Claims 1-6 wherein R^7, R^8 and R^9 are the same or different and are selected from $-R^{10}$ and $-L-R^{10}$ wherein R^{10} is

selected from: neutral groups that reduce water solubility; polar groups that increase water solubility; target bonding groups such as functional groups that can be used in labelling reactions; reactive groups; electron donating and withdrawing groups that shift the absorption and emission wavelengths of the photochromic molecule; lipid and hydrocarbon solubilising groups; and L is selected from the group consisting of a straight or branched C_{1-10} alkyl chain, a C_{2-10} monoether or polyether and a C_{2-10} atom chain containing up to two secondary amide linkages.

8. A compound according to any of Claims 1-7 wherein R^{10} is selected from: hydrogen, halogen, amide, C_1-C_6 alkoxy, cyano, aryl, heteroaryl, sulphonate, quaternary ammonium, hydroxyl, optionally substituted amino, sulphydryl, carbonyl, and reactive groups, for example, succinimidyl ester, anhydride, haloacetamide, maleimide, phosphoramidite, hydrazide and carbodiimide; and groups reactive with amino, hydroxyl, carboxyl, aldehyde, or sulphydryl groups.

9. A compound according to Claim 1 selected from:

i) E-4-Dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

ii) E-4-Diphenylmethylene-3-[1-(2,5-dimethyl-3-thienyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

iii) E-4-Dicyclopropylmethylene-7,8-dimethyl-3-[1-(2-methyl-5-phenyl-3-thienyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

iv) E-3-Adamantylidene-7,8-dimethyl-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one;

v) E-3-Adamantylidene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]-benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid;

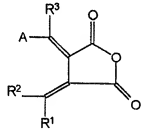
vi) E-8-Amino-4-dicyclopropylmethylene-3-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

vii) Z-4-Adamantylidene-8-nitro-3-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one;

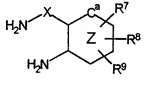
viii) Phenacyl Z-3-dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylate;

ix) E-3-Dicyclopropylmethylene-4-[1-(2,5-dimethyl-3-furyl)ethylidene]benzimidazol[1,2-a]pyrrolidin-2-one-8-carboxylic acid.

10. A method for producing a compound according to any of Claims 1-9 comprising reacting a compound of formula:



or its corresponding di-carboxylic acid, di-C_1 - C_6 alkyl ester, or mono-carboxylic acid-mono C_1 - C_6 alkyl ester derivative, wherein R^1, R^2, R^3 and A are as hereinbefore defined with a compound of formula:



or a salt thereof, optionally substituted by groups R^7, R^8 and R^9, wherein R^7, R^8, R^9, X and Z are as hereinbefore defined.

11. A method of imparting photochromic properties to a non-polar material, the method comprising the step of admixing the non-polar material with a compound as recited in any one of Claims 1-9, wherein at least one groups R^7, R^8 and R^9 is an uncharged group.

12. A method of imparting photochromic properties to a polar material, the method comprising the step of admixing the polar material with a compound as claimed in any one of claims 1-9 wherein at least one of the groups R^7, R^8 and R^9 is selected from the group consisting of charged groups and polar groups.

13. A method for imparting photochromic properties to a target material, the method comprising the steps of incubating:

i) a target material having at least one functional group selected from the group consisting of amino, hydroxyl, carbonyl and sulphydryl groups; or having at least one reactive group that can covalently bond with said at least one functional group, and;

ii) an amount of the photochromic compound as claimed in any one of claims 1-9 wherein at least one of groups R^7, R^8 and R^9 is a functional group selected from the group consisting of amino, hydroxyl, carbonyl and sulphydryl; or wherein at least one of groups R^7, R^8 and R^9 is a reactive group that can covalently bond with said at least one functional group;

for a period of time sufficient to permit said at least one functional or reactive group of said fluorescent compound to covalently bond to said at least one reactive or functional group of said target material.

14. A target material covalently labelled with a compound according to any one of claims 1-9.

Fluorescence Study of Photochromic Compound-Fluor Switch

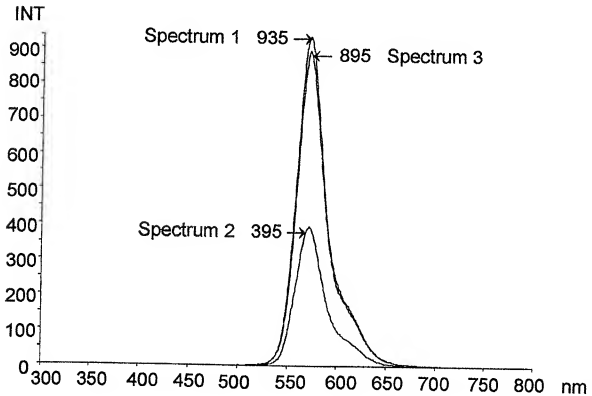


Fig. 1

INTERNATIONAL SEARCH REPORT

Internati ⊿ Application No
PCT/EP 98/08058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 G03C1/73 //(C07D487/04,235:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D G03C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 220 708 A (HELLER) 2 September 1980 cited in the application see claim 1	1,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1999	03/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati ...al Application No
PCT/EP 98/08058

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